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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/661,927	DOWER ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,14-16,25-35,37,40,46-50,52-54,56,58,66 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1 (in part), 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65, 67, 69-77.

DETAILED ACTION

Status of the Application

1. The Response filed December 1, 2003 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-137 were pending. Applicants canceled claims 78-137 and amended claims 1, 3, 14, 27-28, 34-35, 37 and 48. Therefore, claims 1-77 are pending.

4. Claims 1 (in part), 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65, 67, 69-77 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 1-3, 14-16, 25-35, 37, 40, 46-50, 52-54, 56, 58, 66 and 68 are examined on the merits in this action.

6. Please note that this application contains claims drawn to a nonelected invention(s) (e.g., claims 41-45). This was addressed in the previous action (see Paper No. 12, page 3, paragraph 3, Group IV). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Information Disclosure Statement

7. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Withdrawn Objections/Rejections

8. The rejection under 35 U.S.C. 112, second paragraph is hereby withdrawn in view of Applicants' arguments and/or amendments. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 14-16, 25-35, 37, 40, 46-50, 52-54, 56, 58, 66 and 68 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35

USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 1 outlines method steps for screening a "ligand" comprising both a "compound" and a "reporter" that binds to a "carrier-type transport protein" wherein a "populations of cells" expresses said transport protein. The scope of this claim includes an infinite number of methods for producing an infinite number of structural variants (e.g., an infinite number of ligands, an infinite number of compounds, an infinite number of reporters, an infinite number of carrier-type transport proteins) wherein no distinguishing structural attributes are provided for the members of the ligands, compounds, reporters and carrier-type transport proteins. For example, the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "compounds" or "reporters" that comprise the ligands. Although the specification discloses many possible "ligands" and "carrier-proteins" that "might" be used (e.g., see Specification, pages 9-10; see also 35 USC 102 rejections below), the specification and claims do not provide ***any*** guidance as to what structural features ***all*** of these ligands, compounds, reporters, carrier-proteins share.

Please also note that the "protein" and "ligand" are only defined using functional language e.g., the proteins ability to act as a "carrier" or the ligands ability to bind to a carrier-type transport protein (see also 35 USC 112, second paragraph rejection below). With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by

structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. Similarly, the instant claims define the components of the claimed invention only by their functional properties (e.g., "ability to act as a transporter or ability to bind a protein")(emphasis provided). The CAFC held this sort of functional definition insufficient to adequately describe the claimed product.

Consequently, it is not possible to determine *a priori* which ligands, compounds, reporters, carrier-proteins would be encompassed by Applicants' broad claims because there is no common structural attributes that can link together ***all*** of these potential ligands, compounds, reporters, and carrier proteins i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of ligands, compounds, reporters, carrier-proteins that should be included in this genus from the few examples provide by applicants. For example, not all carrier-type transport proteins can be used for screening because they do not possess the requisite "wide substrate specificity" that is critical to Applicants' claimed method and Applicants specification does not provide any guidance as to which of the carrier-type transport proteins would be amendable to such a method. Furthermore, even if a carrier-type transport protein does possess the required wide substrate specificity, the "reporter" that is bound to the compound that is being screened can "prevent" the assay from occurring for "all" compounds that are attached to said reporter. For example, the reporter may be degraded once it is

internalized within the cell or it may prevent all ligands from being transported because the substrate specificity of the enzyme will not accommodate the reporter.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples like dipeptide transporter, oligopeptide transporter, simple sugar transporter (e.g., see Specification, pages 9-10; see also page 32, last paragraph) is insufficient to teach the entire genus. A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

With respect to adequate disclosure applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat*_(CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited

above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Here, Applicants' only working examples are generally directed toward the use of either a dipeptide library against a PEPT1 transporter or a glycocholic acid library against a ASBT bile acid transporter library that are known to have broad substrate specificity (see Specification, Examples; see also 35 U.S.C. § 102 rejections below). These examples, however, do not "teach" the enormous and highly variant genus that is currently claimed. Furthermore, the "laundry list" of other species cited in the specification (e.g., see Examples; see also pages 9-10, 28-30 and 32) because this "laundry list" would not lead a person of skill in the art to any particular species (e.g., see Fujikawa v. Wattanasin, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); see also In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Response

10. Applicant's arguments directed to the above Written Description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that they have submitted a representative number of species (e.g., see 12/1/2003 Response, pages 18-19).

[2] Applicants argue that they are claiming a "method" and, as a result, the do not need to adequately describe the materials used in that method (e.g., see page 19, last paragraph).

[3] Applicants argue, "Structural details beyond those provided in the current claims and specification are not required because screening methods by definition involve the analysis of widely divergent compounds to identify the limited number of compounds having the desired activity. If the claims are deemed to encompass compounds of divergent structure, this is a reflection of the fact that the essence of a screening method lies in the ability to screen a large number of distinct molecules" (e.g., see page 20, paragraph 2).

[4] Applicants argue that Lilly was limited to nucleic acids and thus is not applicable here (e.g., see 12/1/2003 Response, page 20, paragraph 3).

[5] Applicants argue the "a priori" standard is wrong and that this standard is inapplicable to the current claims (e.g., see 12/1/2003 Response, pages 20-21).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants have only set forth a "laundry list" of "potential" species that will not adequately describe the broad scope of Applicants claimed invention because this "laundry list" would not lead a person of skill in the art to any particular species (e.g., see Fujikawa v. Wattanasin, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); see also In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

[2] The Examiner contends that "method" claims also must be adequately described. (e.g., see University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 926 (Fed.Cir.2004)) ("Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.").

[3] The Examiner notes that Applicants have misconstrued the Examiner's arguments with respect to the written description rejection. The Examiner is NOT arguing that a wide variety of divergent compounds cannot be screened as Applicants purport. As outlined in the amended rejection above, the Examiner is contending that not all carrier-type transport proteins can be used for screening because they do not possess the requisite "wide substrate specificity" that is critical to the method and Applicants specification does not provide any guidance as to which of the transporter proteins would be amendable to such a method. Furthermore, even if a carrier-type transport protein does possess the required wide substrate specificity, the "reporter" that is bound to the compound that is being screened can "prevent" the assay from occurring for "all" compounds (i.e., whether they are a diverse set of compounds or not does not matter) that are attached to said reporter. For example, the reporter may be degraded once it is internalized within the cell or it may prevent all ligands from being transported because the substrate specificity of the enzyme will not accommodate the reporter.

[4] The Examiner contends that this narrow reading of Lilly is unwarranted and has been rejected by the CAFC (e.g., see University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 927 (Fed.Cir.2004)) ("As we held in Lilly, "[a]n adequate written description of a DNA . . .

'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." 119 F.3d at 1566 (quoting Fiers, 984 F.2d at 1171). For reasons stated above, that requirement applies just as well to non-DNA (or -RNA) chemical inventions").

[5] The Examiner is not applying an "*a priori*" standard and, as a result, Applicants arguments are moot. The Examiner is applying the standard set forth in the MPEP § 2163 i.e., the specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (e.g., see MPEP § 2163). Here, the Examiner provides further evidence in the "a priori" section that Applicants have not met this standard.

Furthermore, the Examiner notes again that Applicants have misconstrued the Examiner's rejection when they state that "one simply cannot know, in fact one does not want to know, *a priori* the detailed chemical structure of the compounds to be screened" (i.e., this argument was never made by the Examiner; see section **[3]** above). As outlined in the amended rejection above, the Examiner is contending that not all carrier-type transport proteins can be used for screening because they do not possess the requisite "wide substrate specificity" that is critical to the claimed method, nor does Applicants specification provide any guidance as to which of the carrier-type transport proteins would be amendable to such a method. Furthermore, even if a carrier-type transport protein can be found that does possess the required wide substrate specificity (e.g., dipeptide transporter), the "reporter" that is bound to the compound that is being screened (which can be any compound) can "prevent" the assay from occurring because (1) the

"reporter" may not fall within the "substrate specificity" of the carrier-type transport protein being assayed or (2) the reporter may be rapidly degraded upon entry into the cell.

Accordingly, the Written Description rejection cited above is hereby maintained.

11. Claims 1-3, 14-16, 25-35, 37, 40, 46-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening a library of dipeptides for a PEPT1 dipeptide transporter or a library of glycocholic acid derivatives for the ASBT ileal bile acid transporter, is not enabling for the vast majority of "ligands", "carrier-type transporter complexes" and "population of cells" wherein the ligand is internalized within the population of cells. This is an enablement rejection.

Any person skilled in the art to which it pertains, or with which it is most nearly connected, would not know how to make and use the claimed invention. Applicant has not provided enough examples of how to make and use the claimed invention to be enabling for the full breadth of the claims. It is clear from applicants' specification how one might practice this invention with carrier-type transport proteins that show broad substrate specificity (i.e., the PEPT1 and ASBT transporters) and reporters that are stable and do not interfere with the assayed compounds ability to bind and/or be transported by the transport proteins. However, Applicants have not provided sufficient guidance as to how to make/use ***any*** ligands with ***any*** carrier-type transport protein that are internalized within ***any*** population of cells, especially carrier-type transport proteins that do not show broad specificity (see example below).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: Applicant claims are broad. They read on an infinite number of methods for screening an infinite number of ligands comprising an infinite number of compounds and an infinite number of reporters against an infinite number of carrier-type transport proteins. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: The state of the prior art and the level of predictability in the art is low or absent as exemplified by Abe et al. Abe et al. disclose a library of dipeptide "compounds" that are conjugated to a fluorescent "reporter" (i.e., Flu or Coum) that are used as "ligands" for the PEPT1 dipeptide "carrier-type transport protein" (see Abe et al, abstract; see also Materials and Methods section). However, Abe et al clearly shows that although these dipeptide

ligands bind to the PEPT1 transporters, the transporters do not "transport" the ligands inside the population of cells and that the reason for this anomaly is not known (see Abe et al, page 30, column 1, paragraph 1, "The reasons that this fluorescent dipeptide [citing other similar dipeptides with **different reporter labels** that are transported] is transported and our fluorescent dipeptide is not transported is not known") (emphasis added). Abe et al. also disclose that not all transporters have "a wide substrate specificity", which is a necessary element to obtain meaningful screening results (e.g., see abstract). For example, if a transporter will not transport any other ligands beside the natural ligand then a meaningful screening method cannot be performed. Consequently, the Examiner contends that not all carrier-type proteins can be used in screening methods (i.e., not all carrier-type proteins have wide substrate specificity which is critical to the invention; see also page 24, column 1, paragraph 2 wherein the authors disclose that even Applicants preferred dipeptide/oligopeptide transporters have a limited substrate specificity and thus cannot test all compounds i.e., the "essential structure" of the substrate is disclosed). Furthermore, even if a carrier-type protein does have a wide substrate specificity that will enable a screening method, the fact that some "reporters" will not work for no apparent reason (i.e., all testable compounds conjugated to a particular reporter will not work) adequately demonstrates that the nature of the invention is not predictable. Here, Abe et al demonstrate that one of Applicants preferred conjugate types (i.e., a dipeptide library conjugated to either a Flu or Coum) will NOT be internalized by one of Applicants preferred carrier-type proteins (e.g., PEPT1) and they say that the reason for this lack of

internalization is not known i.e., the art is not predictable even for Applicants preferred embodiments.

Furthermore, Abe et al shows yet another level of unpredictability when they try (and fail) to use (Coum)Lys-Sar and Val-Lys(Coum). Here, the "Coum" label was rapidly degraded inside the cell and, as a result, the researchers were not able to determine the initial uptake of Coum analogous. Consequently, even ligands that are internalized (which often does not happen for no apparent reason, see above) may still not work because their detection labels can be unexpectedly degraded i.e., NO LIGANDS WILL WORK with Coum.

(4) The level of one of ordinary skill: The level of skill required for this invention would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any examples for the vast majority of ligands, carrier-type transport proteins and cell types that fall within the scope of these broad claims. Furthermore, there is no generic strategy for **[a]** determining which transport proteins have a limited specificity (and hence will not work) from those that have a broader specificity (see Abe et al, page 24, column 1, paragraph 1 discussing specificity requirements) **[b]** determining which reporters will prevent the complex from binding to the transport proteins (and hence will not work) from those reporters that permit binding, **[c]** determining which reporters will bind to the transport proteins but nevertheless prevent uptake (and hence will not work, at least for the full scope of Applicants claims which includes internalization) from those that will allow transport (see Abe et al, page

30, column 1, paragraph 1 stating that reporter molecules can at times unexpectedly (i.e., unpredictably) prevent uptake in a cell for no known reason) or **[d]** determining which reporters will be degraded in a particular host cell (and hence will not work) from those that are stable (see Abe et al, page 29, column 2, paragraph 3 showing that some reporters can be unexpectedly degraded by a particular host cell).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification for all the reasons asserted above does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed compounds. The Examiner contends that Applicants few examples do not teach the entire genus because the genus is broad and highly variant and because Applicants few working examples cannot be extrapolated to encompass a broader scope because Applicants have provided no generic strategy that would enable such an extrapolation and Abe et al shows that even embodiments that are closely related to Applicants do not work. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Please note that the Abe et al reference is cited here only to show that Applicants are not enabled for the "full scope" of their claimed invention i.e., the above rejection is a scope rejection, which indicates, that a portion of applicant's invention is indeed enabled by the specification, but points out that a much larger portion of the claimed invention is not enabled. Accordingly, in this respect an enablement rejection for scope is not internally or legally inconsistent with a finding that enabled embodiments are indeed either anticipated or rendered obvious by the prior art (see 35 U.S.C. § 102 rejections below).

Response

12. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Those conducting screening analyses understand that the vast majority of the compounds being screened will not have the desired activity ... the primary goal in a typical screening method is to rapidly assay a diverse collection of compounds to identify the limited number that have the desired activity. By requiring the Applicants identify in advance what complexes are likely to be a ligand for a transport protein, the Office negates the purpose of the screening method ... Those conducting screening methods recognize that as a matter of course that many different large populations of complexes must be prepared and then assayed to identify those complexes with the desired activity. Thus, it does not follow that because many or

most of the complexes might not be active that the enablement requirement is not satisfied" (e.g., see 12/1/2003 Response, pages 21-22).

This is not found persuasive for the following reasons:

First, the Examiner notes that Applicants have not addressed the majority of the Wands factors set forth in the original rejection (e.g., 1-2 breadth of claims) and, as a result, Applicants concede these factors. Second, the Examiner notes that Applicants have misconstrued the Examiner's arguments with respect to the unpredictability in the art and have also failed to address the Abe reference set forth in the rejection. The Examiner is NOT arguing "because many or most of the complexes [that are being screened] might not be active that the enablement requirement is not satisfied" as Applicants contend (see above). The Abe reference was set forth to show that the art is unpredictable. As outlined in the amended rejection above, the Examiner is contending that not all carrier-type transport proteins can be used for screening because they do not possess the requisite "wide substrate specificity" that is critical to the claimed method, nor does Applicants specification provide any guidance as to which of the carrier-type transport proteins would possess the required "wide substrate specificity" (i.e., if a carrier-type transport protein can only transport one compound then it cannot be used for a screening method which requires multiple compounds). Furthermore, even if a carrier-type transport protein can be found that does possess the required wide substrate specificity (e.g., dipeptide transporter), the "reporter" that is bound to the compound that is being screened (which can be any compound) can "prevent" the assay from occurring because (1) the "reporter" may not fall within the "substrate specificity" of the carrier-type transport protein being assayed or (2) the reporter may

be rapidly degraded upon entry into the cell, which are both exemplified by the Abe et al. reference.

Accordingly, the Enablement rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 2, 35, 37, 56, 58, 66 and 68 are rejected under 35 U.S.C. 102(a) as being anticipated by Abe et al (Abe, H.; Satoh, M.; Miyauchi, S.; Shuto, S.; Matsuda, A.; Kamo, N. "Conjugation of Dipeptide to Fluorescent Dyes Enhances its Affinity for a Dipeptide Transporter (PEPT1) in Human Intenstinal Caco-2 cells" *Bioconjugate Chem.* **December 31, 1998** (on web), *10*, 24-31) (IDS Paper No. 8, Ref. No. 7).

For ***claims 1, 35, 56, 58, 66***, Abe et al (see entire document) discloses a method for screening for fluorescent dipeptide conjugate ligands to the Dipeptide Transporter (PEPT1) protein, which anticipates claim 1. For example, Abe et al discloses **[a]** providing a library comprising different complexes (e.g., Val-Lys or Lys-Sar conjugated to fluorescein isothiocyanate (Flu) or coumarin-3-carboxylic acid (Coum) and [^{14}C]Gly-

Sar, see page 24, column 2, paragraph 1; see also page 27, "Uptake Experiments in Monolayer Caco-2 Cells" section), each complex comprising a compound (e.g., Val-Lys, Lys-Sar, Gly-Sar) and a reporter (e.g., Flu, Coum, [^{14}C]) the compound varying between different complexes (Val-Lys, Lys-Sar, Gly-Sar are not the same). Furthermore, Abe discloses **[b]** providing a population of cells, one or more of which expresses one or more carrier type proteins (see Abe et al, Title disclosing the Dipeptide Transporter (PEPT1) in Human Intestinal Caco-2 Cells). Abe et al also discloses **[c]** contacting the population of cells with a plurality of complexes from the library (see Abe et al, page 30, column 1, paragraph 1, "the fluorescent analogues can bind the binding site of the transporter"; see also Figure 1 showing simultaneous addition of Gly-Sar with Val-Lys(Flu) or (Flu)Lys-Sar). Finally, Abe et al discloses **[d]** detecting a signal from the reporter of a complex that is bound to a cell or internalized within a cell, the signal providing an "indication" that a complex whose reporter generated the signal comprises a compound that is a ligand for a carrier-type transport protein (see Abe et al, page 29, column 1, paragraphs 4-6 disclosing both fluorescence detection and detection of radioactivity). Please note that Applicants claims do not require that the compound is actually a substrate, but only that the signal provided by the internalized reporter provide an "indication" that it might be. Here, if Flu uptake did not provide an "indication" that the conjugates were substrates for the transporters then the kinetic analysis would not have been performed because there would have been no need to perform the analysis.

Furthermore, in Abe et al. the (Flu)Lys-Sar and Val-Lys(Flu) reporters (i.e., the "Flu" reporters) "preferentially generate a signal" with respect to the (Coum)Lys-Sar and

Val-Lys(Coum) reporters (i.e., the "Coum" reporters) only when they are "internalized within the cell" because unlike the "Flu" reporters, the "Coum" reporters were "rapidly degraded to coumarin-3-carboxylic acid inside [the] cells" and, as a result, the initial uptake of "Coum" analogues was unable to be determined (see Abe et al., page 29, column 1, paragraph 4).

For ***claim 37***, Abe et al discloses different reporters e.g., Flu or Coum and [^{14}C].

Response

14. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Abe does not discuss a method in which a reporter preferentially generates a signal once it is internalized. For example, there is no indication in the Abe reference that the fluorescent or radioactive labels utilized in his experiment would preferentially generate a signal one incorporated into a cell expressing a carrier-type transport protein. Abe thus fails to teach each and every aspect of the current claims." (e.g., see 12/1/2003 Response, page 23, paragraph 4).

This is not found persuasive for the following reasons:

The Examiner contends that Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without

specifically pointing out how the language of the claims patentably distinguishes them from the references. Applicants state that the Abe reference provides "no indication ... that the fluorescent or radioactive labels utilized in his experiment would preferentially generate a signal once incorporated into a cell" (see above), but they provide no rationale to support their assertion.

Furthermore, to the extent that the rationale set forth in Applicants' response to Swan et al could be applied here i.e., that the reporter in Abe would be expected to give "the same type of signal whether located outside or inside the cell" and thus would not anticipate the newly amended claim (e.g., see 12/1/2003 Response, page 24, paragraph 1), the Examiner contends that Applicants arguments are not commensurate in scope with the claims. Nowhere in newly amended claim 1 does it state that the reporter is being compared to itself with respect to its ability to generate a signal once it is internalized within the cell (i.e., reporter A can "preferentially generate a signal" with respect to reporter B [i.e., a different reporter], which is exactly the case that is exemplified by Abe). In Abe, the (Flu)Lys-Sar and Val-Lys(Flu) reporters (i.e., reporter A) "preferentially generate a signal" with respect to the (Coum)Lys-Sar and Val-Lys(Coum) reporters (i.e., reporter B) only when they are "internalized within the cell" because unlike (Flu)Lys-Sar and Val-Lys(Flu), the (Coum)Lys-Sar and Val-Lys(Coum) were "rapidly degraded to coumarin-3-carboxylic acid inside [the] cells" (see Abe et al., page 29, column 1, paragraph 4). Thus, Abe does anticipate every limitation in the claim.

Accordingly, the 35 U.S.C. §102(a) rejection cited above is hereby maintained.

15. Claims 1-3, 14, 35, 56 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Swaan et al (Swaan, P. W.; Hillgren, K. M.; Szoka, F. C.; Oie, S. "Enhanced Transepithelial Transport of Peptides by Conjugation to Cholic Acid" *Bioconjugate Chem.* **1997**, *8*, 520-525).

For ***claims 1, 35, 56, 66***, Swaan et al (see entire document) discloses screening radiolabeled [^{3}H]bile acid-peptide conjugates against a bile acid transporter expressed in CaCo-2 cells, which anticipates claim 1 (see Swaan et al, abstract, figures 1-2 wherein the "compounds" = the different peptides; the "reporter" = [^{3}H]bile acid; the "population of cells" = CaCo-2; the "signal" = radioactivity).

For ***claims 2-3, 14***, Swaan et al discloses the enzymatic cleavage via cellular peptidases of the [^{3}H]bile acid-peptide conjugate into [^{3}H]cholic acid (see Swaan et al, figure 4). In this scenario, the radioactive [3H]cholic acid signal is preferentially generated only when the reporter is internalized within the cell.

Response

16. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Swaan also fails, however, to discuss a method in which a reporter preferentially generates a signal once it is internalized. To the contrary, the radioactive label

used in Swaan would be expected to give the same type of signal whether located outside or inside the cell" (e.g., see 12/1/2003 Response, paragraph bridging pages 23-24).

This is not found persuasive for the following reasons:

The Examiner contends that arguments are not commensurate in scope with the claims. Nowhere in newly amended claim 1 does it state that the reporter must generate a different "type" of signal inside the cell as opposed to outside the cell. Furthermore, newly amended claim 1 does not state that the reporter is being compared to itself with respect to its ability to generate a signal once the reporter is internalized within the cell. However, even if *assuming arguendo* that Applicants arguments were read into the claim (which they're not), the newly amended claim would still be anticipated. For example, the [3H]bile acid reporter generates a signal at approximately ~3.1 min (e.g., see figure 4) when the reporter is metabolized (i.e., internalized within the cell and enzymatically degraded from [3H]bile acid-peptide conjugate to [3H]cholic acid). In this scenario, the first signal type i.e., the radioactive signal generated by the [3H]bile acid-peptide conjugate is converted into the second signal type i.e., the radioactive signal generated by [3H]cholic acid after the reporter is internalized within the cell. Thus, the reporter does not generate the same "type" of signal whether it is located outside the cell as purported by Applicants.

Accordingly, the 35 U.S.C. §102(b) rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-3, 14, 35, 56, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swaan et al (Swaan, P. W.; Hillgren, K. M.; Szoka, F. C.; Oie, S. "Enhanced Transepithelial Transport of Peptides by Conjugation to Cholic Acid" *Bioconjugate Chem.* **1997**, *8*, 520-525) and Dawson et al (U.S. Patent No. 5,589,358) (Date of Patent is **December 31, 1996**) (IDS Paper No. 8, Ref. No. 2).

For ***claims 1-3, 14, 35, 56 and 66***, Swaan et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-3, 14, 35, 56 and 66 and, consequently, also renders obvious claims 1-3, 14, 35, 56 and 66.

The prior art teaching of Swaan et al differs from the claimed invention as follows:

For ***claim 68***, the prior art teachings of Swaan et al differs from the claimed invention by not specifically reciting the use of a "control" (see Swaan et al,).

However, Dawson et al teaches the following limitations that are deficient in Swaan et al:

For ***claim 68***, Dawson et al (see entire document) teaches that cells expressing bile acid transporters can be used in high throughput screening with "controls" (see Dawson et al, column 22, paragraph 2-3).

It would have been obvious to one skilled in the art at the time the invention was made to use the screening method as taught by Swaan et al with the "controls" as taught by Dawson et al because Dawson et al teaches that "controls" are useful for obtaining accurate results. Furthermore, one of ordinary skill in the art would have been motivated to use "controls" so that more accurate measurements could be obtained.

Response

20. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Dawson fails to remedy the deficiencies in the disclosure of Swaan. In particular, neither of these cited references teaches or suggests a screening method in which a reporter preferentially generates a signal once it becomes incorporated into the cell.

Accordingly, it is submitted that the claims are not prima facie obvious" (e.g., see 12/1/2003 Response, page 24, paragraph 3).

This is not found persuasive for the following reasons:

The Examiner contends that the Swaan reference is not deficient as suggested by Applicants because it does teach a reporter that preferentially generates a signal once it becomes incorporated into the cell (e.g., see "Response" to Applicants arguments above under the 35 U.S.C. § 102(b) rejection for Swaan, which are incorporated herein in their entirety by reference).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
March 17, 2004